

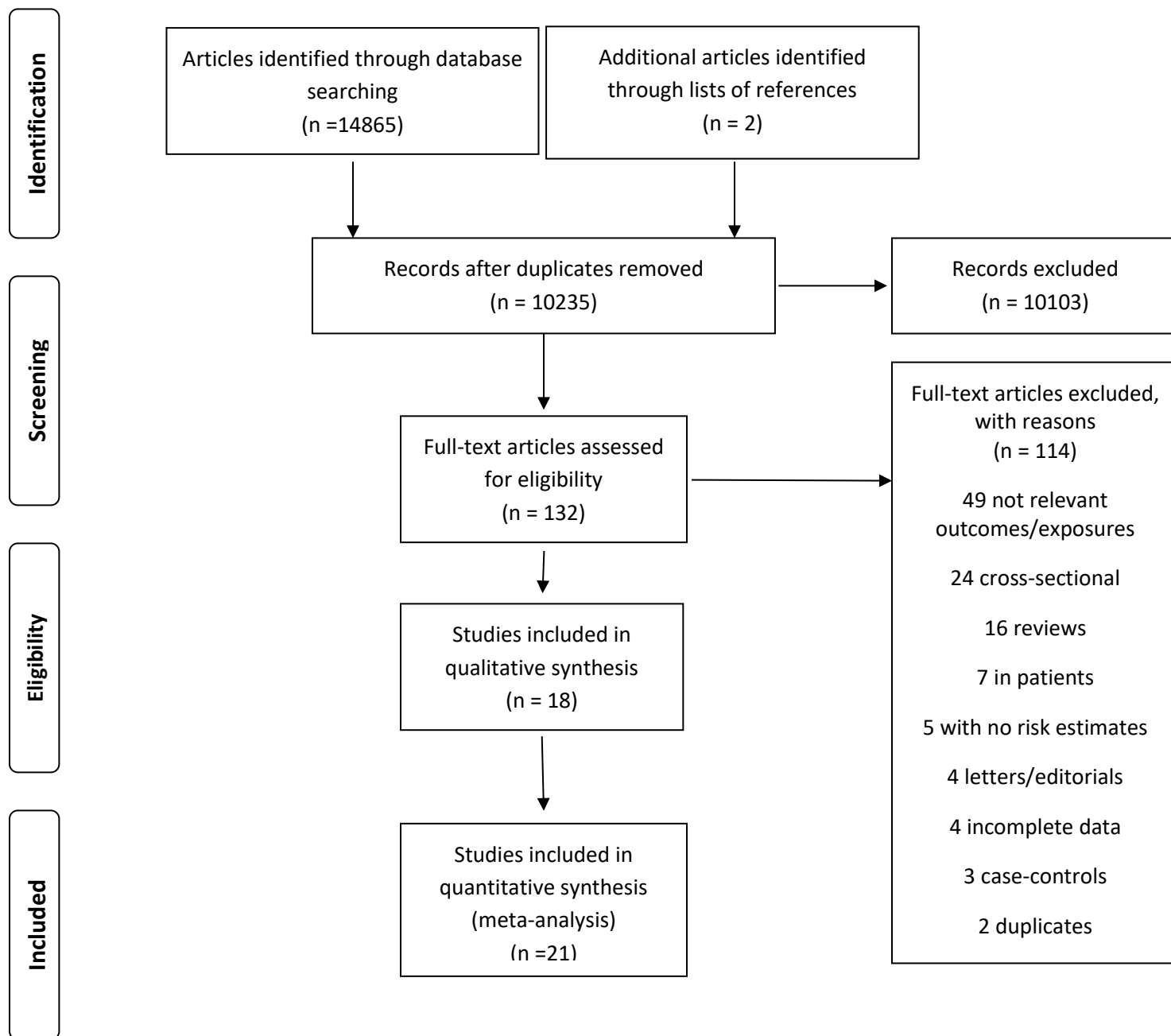
**Inflammation Markers and Risk of Developing Hypertension: a Meta-Analysis of Cohort  
Studies**

**Online Supplementary file 1.** Search strategy to find the relevant articles for inclusion in meta-analysis of inflammation markers and risk of hypertension.

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| <b>PubMed</b>  |
| 1. C-reactive protein (MeSH)/ OR interleukins (MeSH)/ OR interleukin-6 (MeSH)                    |
| 2. interleukin-1beta (MeSH)/ OR IL-6 (Title/Abstract)/ OR IL-1 $\beta$ (Ti/Ab)                   |
| 3. CRP (Ti/Ab)/ OR high-sensitive c-reactive protein (Ti/Ab)/ OR hs-CRP (Ti/Ab)                  |
| 4. inflammatory (Ti/Ab)  |
| 5. Hypertension (MeSH)/ OR blood pressure (MeSH)   |
| 6. HTN (Ti/Ab) or high blood pressure (Ti/Ab)  |
| 7. cohort studies (MeSH)/ OR longitudinal studies (MeSH)/ OR observational studies (MeSH)/       |
| 8. prospective studies (MeSH)/ OR retrospective studies (MeSH)                                   |
| 9. prospective (Ti/Ab)/ OR r prospectively (Ti/Ab) OR longitudinal (Ti/Ab)                       |
| 10. cohort (Ti/Ab)/ OR cohorts (Ti/Ab)/ OR observation (Ti/Ab)                                   |
| 11. observational (Ti/Ab)/ OR follow up (Ti/Ab)/ OR nested (Ti/Ab)                               |
| 12. retrospective (Ti/Ab)/ OR relative risk (Ti/Ab)/ OR RR (Ti/Ab)                               |
| 13. hazard ratio (Ti/Ab)/ OR HR (Ti/Ab) OR odds ratio (Ti/Ab)                                    |
| 14. 1 OR 2 OR 3 OR 4   |
| 15. 5 OR 6   |
| 16. 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13  |
| 17. 14 AND 15  |
| 18. 16 AND 17  |
| <b>Scopus</b>  |
| 1. Inflammatory (Article title, Abstract, Keywords)/ OR inflammation (ti/Ab/Ke)                  |
| 2. C-reactive protein (ti/Ab/Ke)/ OR CRP (ti/Ab/Ke)/ OR hs-CRP (ti/Ab/Ke)                        |
| 3. high-sensitive c-reactive protein (ti/Ab/Ke)/ OR interleukin-6 (ti/Ab/Ke)/ OR IL-6 (ti/Ab/Ke) |
| 4. interleukin-1 beta (ti/Ab/Ke)/ OR IL-1 $\beta$ (ti/Ab/Ke)                                     |
| 5. hypertension (ti/Ab/Ke)/ OR HTN (ti/Ab/Ke)/ OR blood pressure (ti/Ab/Ke)                      |
| 6. prospective (ti/Ab/Ke)/ OR prospectively (ti/Ab/Ke)/ OR longitudinal (ti/Ab/Ke)               |
| 7. cohort (ti/Ab/Ke)/ OR cohorts (ti/Ab/Ke)/ OR observation (ti/Ab/Ke)                           |
| 8. observational (ti/Ab/Ke)/ OR follow-up (ti/Ab/Ke)/ OR nested (ti/Ab/Ke)                       |
| 9. retrospective (ti/Ab/Ke)/ OR relative risk (ti/Ab/Ke)/ OR RR (ti/Ab/Ke)                       |
| 10. hazard ratio (ti/Ab/Ke)/ OR HR (ti/Ab/Ke)/ OR odds ratio (ti/Ab/Ke)                          |
| 11. 1 OR 2 OR 3 OR 4   |
| 12. 6 OR 7 OR 8 OR 9 OR 10   |
| 13. 5 AND 11   |
| 14. 12 AND 13  |

**Online Supplementary file 2.** Detailed method to translate reported risk estimates in the primary studies to the third versus first tertile.

For studies that categorized the exposure in tertiles of the inflammation marker, the risk ratios (RRs) were included in the meta-analysis as reported. For studies that categorized the exposure in quartile/quintile of the marker, or reported the results as continuous, we used method introduced by Danesh and colleagues to convert the RRs from original studies to the RR for the third vs. first tertile. [20] According to this method, for studies that reported the RR for an increment of 1-SD in the level of the inflammation marker, we used a scaling factor of 2.18 to obtain the RR for the third vs. first tertile. The factor of 2.18 is the difference in the means of the upper and lower tertile of the standard normal distribution. Also, the factors of 2.54 and 2.80 are the difference in the means of the upper and lower quartiles and quintiles of the standard normal distribution, respectively. Thus, this scaling method assumes that the exposure follows a normal distribution and the association with disease risk (hypertension) is log-linear. For studies that grouped the exposure in quartiles, we used a scaling factor of  $2.18/2.54$  to translate the RR for the top vs. the bottom quartile to the RR for the third vs. first tertile. Similarly, a scaling factor of  $2.18/2.80$  was used to translate the RR for the top vs. the bottom quintiles to the RR for the third vs. first tertile. For studies that reported the RR per 1-unit increment of the marker, we exponentiated the  $\log(RR)$  times the study-specific SD of the marker, to get the RR for an increment of 1-SD in the level of the marker, and then converted this RR to a RR for the third vs. first tertile using a scaling factor of 2.18. If the SD was not reported, we calculated the average difference between the mid-point of the marker in the third and first tertiles, from other studies, and then applied the per-unit RR to the average difference to obtain the RR for the third vs the first tertile.



**Online Supplementary file 3.** Literature search and study selection process to find the potential relevant studies for inclusion in the meta-analysis of inflammation markers and risk of developing hypertension.

**Online Supplementary file 4.** General characteristics of the studies included in meta-analysis of circulating inflammation markers and risk of developing hypertension.

| Author name, publication year | Study name, country                                   | Study design, (Follow-up duration, years) | Age (range, mean; years) | Cases/ participants (controls) | Gender | Marker (comparison)   | Hypertension definition   | Quality score (max. 9 points) |
|-------------------------------|---|---|--------------------------|--------------------------------|--------|---|---|-------------------------------|
| Lakoski, 2011 [7]             | Multi-Ethnic Study of Atherosclerosis (MESA), US      | Prospective cohort (5)                    | 45-84 (59)               | 714/3543                       | W/M    | CRP ( $\geq 3.69$ vs. $0.71$ mg/L)<br>IL-6 ( $\geq 1.69$ vs. $<0.68$ pg/mL) | BP $\geq 140/90$ mm Hg or use of blood pressure medications   | 8                             |
| Sesso, 2003 [8]               | Women's Health Study, US                              | Prospective cohort (7.8)                  | $\geq 45$ (53)           | 5365/20525                     | W      | CRP ( $5.75$ vs. $0.27$ mg/L)   | New physician diagnosis of hypertension, the initiation of medication for elevated BP, or self-reported SBP $\geq 140$ mm Hg or DBP $\geq 90$ mm Hg | 8                             |
| Sung, 2017 [9]                | Samsung Hospital Health Screening Center study, Korea | Retrospective cohort (3.3)                | $\geq 18$ (37)           | 10405/<br>96,606               | W/M    | CRP (M: $\geq 1.2$ vs. $<0.4$ mg/L,<br>W: $\geq 0.9$ vs. $<0.2$ mg/L)       | Use of antihypertensive medications, or if the average of two measurements of SBP was $\geq 140$ mm Hg or DBP $\geq 90$ mm Hg                       | 8                             |

# Supplementary Files

|                      |   |                          |            |          |     |                            |   |   |
|----------------------|---|--------------------------|------------|----------|-----|----------------------------|---|---|
| Dauphinot, 2009 [10] | Proof study, France   | Prospective cohort (2)   | 66         | 33/335   | W/M | CRP* (1 mg/L)              | Systolic ABMP of at least 135 mm Hg or diastolic ABMP of at least 85 mm Hg or use of antihypertensive medications   | 6 |
| Jung, 2014 [11]      | Korean Genome and Epidemiology Study on Atherosclerosis Risk, Korea | Prospective cohort (2.6) | 40-70 (55) | 178/1553 | W/M | hs-CRP* (1 mg/L)           | SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg, and/or the use of antihypertensive medication  | 7 |
| Lakoski, 2006 [12]   | Coronary Artery Risk Development in Young Adults (CARDIA) study, US | Prospective cohort (7)   | 25-37 (32) | 413/3919 | W/M | CRP (>3 vs. <1 mg/L)       | BP of 140/90 mm Hg or greater, or use of BP medications   | 8 |
| Sesso, 2007 [13]     | Women's Health Study, US  | Nested case-control (10) | ≥ 45 (55)  | 400/400  | W   | IL-6 (1.93 vs. 0.48 µg/dL) | Self-reports of a physician diagnosis of hypertension/ self-reports of antihypertensive treatment/ self-reports of SBP ≥140 mm Hg, self-reports of DBP ≥ 90 mm Hg | 8 |

# Supplementary Files

|                   |  |                                  |                |          |     |                               |   |   |
|-------------------|--|----------------------------------|----------------|----------|-----|-------------------------------|---|---|
| Chow, 2007 [14]   | Hong Kong Cardiovascular Risk Factor Prevalence Study, Hong Kong | Nested case-control (5)          | 25-74 (50)     | 70/140   | W/M | hs-CRP* (1 mg/L)              | Sitting BP $\geq$ 140/90 mm Hg or on regular antihypertensive drugs                   | 7 |
| Chuang, 2016 [15] | MJ Health Screening Database, Taiwan                             | Prospective matched cohort (1.6) | $\geq$ 20 (45) | 543/4109 | W/M | CRP* (1 nmol/L)               | SBP $\geq$ 140 mm Hg, DBP $\geq$ 90 mm Hg, or the use of antihypertensive drugs       | 7 |
| Chuang, 2013 [16] | Cardiovascular Disease Risk Factors Two-Township Study, Taiwan   | Prospective cohort (3.27)        | $\geq$ 20 (45) | 145/2113 | W/M | CRP (4.84 vs. 0.46 mg/L)      | SBP $\geq$ 140 mm Hg, a DBP $\geq$ 90 mm Hg, or the use of antihypertensive drugs     | 7 |
| Lee, 2014 [17]    | HYpertension-Diabetes Daegu Initiative (HYDDI) study, Korea      | Prospective cohort (5)           | $\geq$ 20 (53) | 99/452   | W/M | hs-CRP (>0.96 vs. <0.38 mg/L) | SBP $\geq$ 140 mm Hg or a DBP $\geq$ 90 mm Hg, or use of anti-hypertensive medication | 7 |

# Supplementary Files

|                         |  |   |            |          |     |  |  |   |
|-------------------------|--|---|------------|----------|-----|--|--|---|
| Niskanen, 2004 [18]     | Kuopio Ischemic Heart Disease Risk Factor Study, Finland | Prospective cohort (11)                     | 42-60 (51) | 124/379  | M   | hs-CRP (>3 vs <1 mg/L)   | SBP $\geq$ 140 mm Hg, DBP $\geq$ 90 mm Hg, or use of antihypertensive medication                     | 7 |
| Wang, 2011 [26]         | Women's Health Initiative Observational Study, US        | Nested case-control (5.9)                   | < 70 (59)  | 800/800  | W   | IL-6 (White: 2.78 vs. 0.58 pg/mL, Black: 4.39 vs. 0.74)<br>IL-1 $\beta$ (White: 0.48 vs. 0.13 pg/mL, Black: 0.47 vs. 0.13 pg/mL)<br>hs-CRP (White: 4.5 vs. 0.37 mg/L, Black: 7.16 vs. 1.37 mg/L) | The initiation of medication for elevated BP of either SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mm Hg    | 9 |
| Mattace-Raso, 2010 [27] | Rotterdam study, Netherland                              | Prospective cohort (1990-1993 to 2002-2004) | 64         | 252/1637 | W/M | CRP* (1 SD)  | Isolated systolic hypertension (SBP $\geq$ 160 mm Hg and a DBP < 90 mm Hg)                           | 8 |
| Sesso, 2015 [28]        | Physician's Health Study, US                             | Nested case-control (14)                    | 40-84 (47) | 396/396  | M   | CRP ( $\geq$ 1.50 vs. 0.35 mg/L)<br>IL-6 ( $\geq$ 1.31 vs. <0.71 pg/mL)  | Self-reported initiation of antihypertensive treatment, SBP $\geq$ 140 mm Hg, or DBP $\geq$ 90 mm Hg | 8 |



# Supplementary Files

|                       |                                |                          |    |          |     |                                    |   |   |
|-----------------------|--------------------------------|--------------------------|----|----------|-----|------------------------------------|---|---|
| Seven, 2014<br>[29]   | Inter99 study, Denmark         | Prospective cohort (5.4) | 46 | 379/2881 | W/M | CRP* (1 SD)                        | Self-reported use of antihypertensive medication or SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg | 8 |
| Vanhala, 2008<br>[30] | Pieksämäki study, Finland      | Prospective cohort (6.5) | 51 | 128/396  | W/M | IL-1 $\beta$ (0.82 vs. 0.25 pg/mL) | BP $\geq$ 140/90 mm Hg, or antihypertensive drug  | 7 |
| Wang, 2007<br>[31]    | Framingham Offspring Study, US | Prospective cohort (3)   | 56 | 232/1456 | W/M | CRP* (1 SD)                        | SBP $\geq$ 140 mm Hg, DBP $\geq$ 90 mm Hg, or use of antihypertensive medications               | 8 |

\* Inflammation markers were reported as continuous.

Abbreviations: BP, blood pressure; CRP, C-reactive protein; DBP, diastolic blood pressure; hs-CRP, high-sensitive C-reactive protein; IL-1 $\beta$ , interleukin-1 $\beta$ ; IL-6, interleukin-6; M, men; SBP, systolic blood pressure; SD, standard deviation; W, women.

**Online Supplementary file 5.**Reported risk estimates of hypertension in the primary studies in meta-analysis of circulating inflammation markers and risk of developing hypertension.

| Circulating biomarkers categories   | Number of cases/ participants (personyears) | Relative risk (95%CI) | Covariates   |
|---|---|-----------------------|--|
| Chow, 2007 [14]<br>Hong Kong Cardiovascular Risk Factor Prevalence Study, hs-CRP        |   |                       |  |
| log, 1 mg/L   | 70/140                                      | 1.48 (1.07-2.05)      | Age, BMI, mean arterial pressure, triglycerides, fasting insulin, and sex-specific adiponectin.  |
| Chuang, 2013 [16]<br>the Cardiovascular Disease Risk Factors Two-Township Study, CRP    |   |                       |  |
| 0.46 mg/L (median)  | 9.3 (IR/1.000 PY)/ 683                      | 1.00                  | Age, sex, number of metabolic syndrome components, high sodium, and family history of hypertension.  |
| 1.56  | 19.0 (IR/1.000 PY)/ 714                     | 1.43 (0.84-2.41)      |  |
| 4.84  | 33.0 (IR/1.000 PY)/ 716                     | 1.69 (1.02-2.81)      |  |
| Chuang, 2016 [15]<br>MJ Health Screening Database, CRP                                  |   |                       |  |
| 1 nmol/L increment  | 543/4109                                    | 1.02 (1.00-1.04)      | Matched for age and sex and adjusted for physical activity, drinking habit, and study site.  |
| Dauphinot, 2009 [10]<br>the Proof study, CRP  |   |                       |  |
| 1 mg/L increment  | 33/302                                      | 1.17 (0.90-1.52)      | Adjusted for BMI, change in CRP, low density lipoprotein cholesterol, 24-h systolic ambulatory blood pressure, and Change in 24-h systolic ambulatory blood pressure.                    |
| Jung, 2014 [11]<br>Korean Genome and Epidemiology Study on Atherosclerosis Risk, hs-CRP |   |                       |  |
| 1 mg/L increment, Men   | 79/584                                      | 1.01 (0.97-1.04)      | Age, baseline BMI, systolic blood pressure, diastolic blood pressure, smoking, regular exercise, fasting blood glucose, and triglyceride.  |
| 1 mg/L increment, Women   | 99/969                                      | 1.02 (0.97-1.06)      |  |
| Lakoski, 2006 [12]<br>The Coronary Artery Risk Development in Young Adults, CRP         |   |                       |  |
| < 1 mg/L  | 157/1528                                    | 1.00                  | Age, race, BMI, smoking status, ethanol use, low- and high-density lipoprotein cholesterol, history of diabetes, cholesterol-lowering medication use, physical activity, and clinic site |
| 1-3   | 112/876                                     | 1.00 (0.76-1.33)      |  |
| > 3   | 144/848                                     | 1.13 (0.83-1.52)      |  |
| Lakoski, 2011 [7]<br>Multi-Ethnic Study of Atherosclerosis, CRP                         |   |                       |  |
| < 0.71 mg/L   | 132/Q1                                      | 1.00                  | Age, gender, ethnicity, smoking, diabetes, statin use, aspirin use, alcohol use, and MESA study site.  |
| 0.71 to < 1.55  | 162/Q2                                      | 1.00 (0.79-1.26)      |  |
| 1.55 to < 3.69  | 172/Q3                                      | 0.97 (0.77-1.23)      |  |
| ≥ 3.69  | 243/Q4                                      | 1.25 (0.98-1.60)      |  |
| Lakoski, 2011 [7]<br>Multi-Ethnic Study of Atherosclerosis, IL-6                        |   |                       |  |
| < 0.68 pg/mL  | 93/Q1                                       | 1.00                  | Age, gender, ethnicity, smoking, diabetes, statin use, aspirin use, alcohol use, and MESA study site.  |
| 0.68 to 1.05  | 175/Q2                                      | 1.44 (1.11-1.86)      |  |
| 1.05 to 1.69  | 197/Q3                                      | 1.54 (1.19-1.99)      |  |
| ≥ 1.69  | 225/Q4                                      | 1.49 (1.14-1.95)      |  |
| Lee, 2014 [17]<br>The HYPertension-Diabetes Daegu Initiative (HYDDI) study, hs-CRP      |   |                       |  |
| < 0.38 mg/L   | 1.32 ( IR)/151                              | 1.00                  |  |

# Supplementary Files

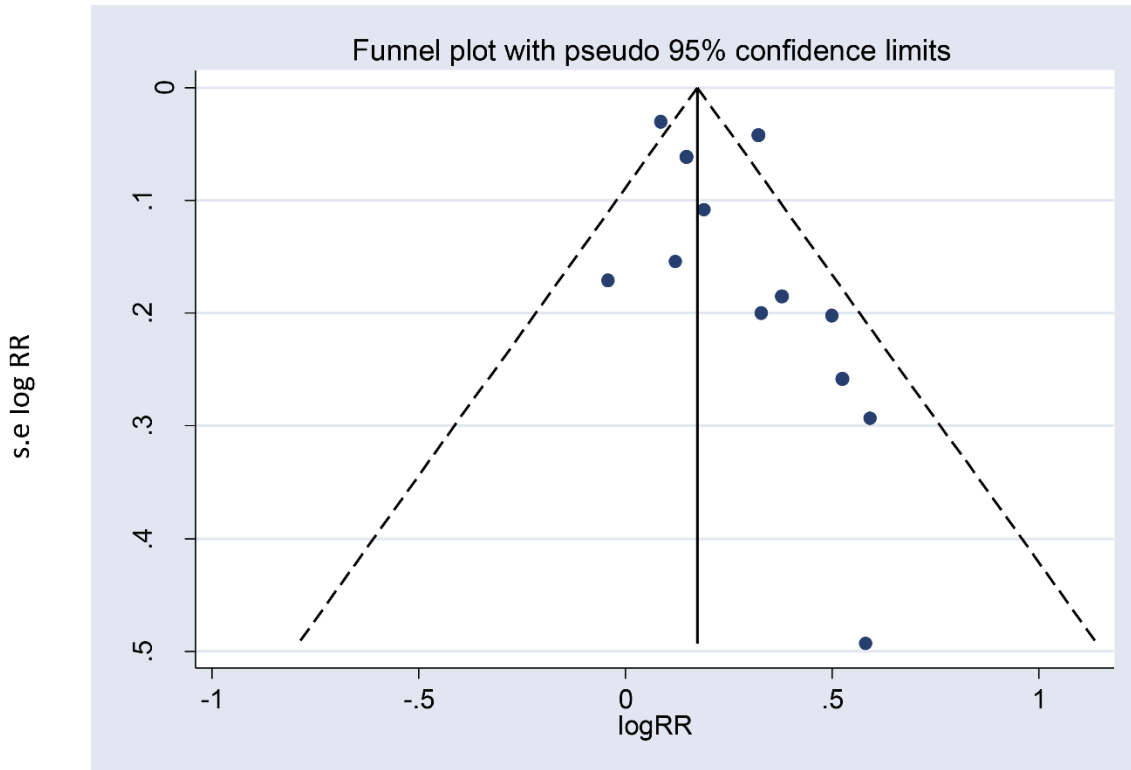
|  |           |                  |   |
|--|-----------|------------------|---|
| 0.38-0.96  | 23.2/151  | 1.83 (0.94-3.57) | Age, gender, body mass index, systolic and diastolic blood pressure, diabetes mellitus, total cholesterol, smoking, drinking and exercise.  |
| > 0.96   | 29.3/150  | 2.33 (1.20-4.52) |   |
| Mattace-Raso, 2010 [27]<br>Rotterdam study, CRP                                |           |                  |   |
| 1 SD increment   | 252/1637  | 1.19 (1.01-1.41) | Age, sex, systolic blood pressure, BMI, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, smoking and leukocyte count.  |
| Niskanen, 2004 [18]<br>Kuopio Ischemic Heart Disease Risk Factor Study, hs-CRP |           |                  |   |
| 0.1-0.99 mg/L  | 210 (n)   | 1.00             | Age, smoking, alcohol intake, adult socioeconomic status, leisure-time physical activity, presence of cardiovascular disease, intake of energy-adjusted dietary factors (dietary intake of saturated fat, sodium, potassium, and fruits and vegetables), baseline systolic blood pressure, waist girth, concentrations of insulin, glucose, high-density lipoprotein cholesterol, and changes in waist girth, smoking , and alcohol intake. |
| 1.0-2.99   | 130       | 1.78 (1.00-3.17) |   |
| 3.0-9.99   | 39        | 2.81 (1.19-6.63) |   |
| Sesso, 2003 [8]<br>Women’s Health Study, CRP                                   |           |                  |   |
| 0.27 mg/L (median)   | 511/3131  | 1.00             | Age, randomized aspirin treatment, randomized vitamin E treatment, randomized beta-carotene treatment, BMI, smoking, exercise, alcohol intake, postmenopausal hormone use, parenteral history of myocardial infarction at younger than 60 years, history of diabetes, and history of high cholesterol.  |
| 0.63   | 673/3379  | 1.07 (0.95-1.20) |   |
| 1.28   | 912/3899  | 1.17 (1.04-1.31) |   |
| 2.44   | 1307/4581 | 1.30 (1.17-1.45) |   |
| 5.75   | 1962/5535 | 1.52 (1.36-1.69) |   |
| Sesso, 2007 [13]<br>Women’s Health Study, IL-6                                 |           |                  |   |
| 0.48 µg/dL (median)  | 59/100    | 1.00             | Matched on age and follow-up time, and adjusted for smoking status, alcohol use, exercise, postmenopausal, postmenopausal hormone use, parental history of myocardial infarction < 60 y, personal history of hypercholesterolemia, history of diabetes, circulating CRP, and BMI.   |
| 0.69   | 76/100    | 1.35 (0.78-2.33) |   |
| 0.94   | 124/100   | 2.01 (1.13-3.57) |   |
| 1.93   | 141/100   | 1.52 (0.81-2.88) |   |
| Sesso, 2015 [28]<br>Physician’s Health Study, CRP                              |           |                  |   |
| < 0.35 mg/L  | Q1        | 1.00             | Matched on age, follow-up time, and date of hypertension, plus adjusted for randomized treatments, smoking status, physical activity, alcohol consumption, parental history of myocardial infarction <60 y, history of high cholesterol and diabetes mellitus, and BMI.   |
| 0.35- to < 0.72  | Q2        | 1.24 (0.80-1.91) |   |
| 0.73 to < 1.50   | Q3        | 1.60 (1.02-2.51) |   |
| ≥ 1.50   | Q4        | 1.47 (0.93-2.32) |   |
| Sesso, 2015 [28]<br>Physician’s Health Study, IL-6                             |           |                  |   |
| < 0.71 pg/mL   | Q1        | 1.00             | Matched on age, follow-up time, and date of hypertension, plus adjusted for randomized treatments, smoking status, physical activity,   |
| 0.71 to < 0.94   | Q2        | 1.08 (0.69-1.69) |   |
| 0.94 to < 1.31   | Q3        | 0.92 (0.59-1.44) |   |

# Supplementary Files

|  |                |                  |   |
|--|----------------|------------------|---|
| ≥ 1.31   | Q4             | 1.36 (0.86-2.13) | alcohol consumption, parental history of myocardial infarction <60 y, history of high cholesterol and diabetes mellitus, and BMI.   |
| Seven, 2014 [29]<br>Inter99 study, CRP   |                |                  |   |
| log, 1 SD increment  | 379/2881       | 0.98 (0.84-1.14) | Age, sex, leptin, adiponectin, alcohol intake, smoking, physical activity, dietary habits, educational level, parental history of hypertension, total cholesterol, triglycerides, insulin, HbA1c, baseline heart rate, and systolic and diastolic blood pressure. |
| Sung, 2017 [9]<br>Samsung Hospital Health Screening Center study, CRP, Men       |                |                  |   |
| < 0.4 mg/L   | 2482/72,773 PY | 1.00             | Age, smoking status, alcohol intake, regular exercise, education level, systolic blood pressure, BMI, and insulin.  |
| 0.4-0.5  | 1494/33,877    | 1.01 (1.02-1.08) |   |
| 0.6-1.1  | 2168/44,725    | 1.12 (1.04-1.19) |   |
| ≥ 1.2  | 2085/42,645    | 1.11 (1.04-1.19) |   |
| Sung, 2017 [9]<br>Samsung Hospital Health Screening Center study, CRP, Women     |                |                  |   |
| < 0.2 mg/L   | 479/44,939 PY  | 1.00             | Age, smoking status, alcohol intake, regular exercise, education level, systolic blood pressure, BMI, and insulin.  |
| 0.2-0.3  | 496/37,287     | 1.06 (0.93-1.22) |   |
| 0.4-0.8  | 532/28,274     | 1.06 (1.01-1.33) |   |
| ≥ 0.9  | 669/31,943     | 1.19 (1.04-1.37) |   |
| Vanhala, 2008 [30]<br>Pieksämäki study, IL-1β                                    |                |                  |   |
| 0.25 pg/mL (median)  | Q1             | 1.00             | Age, gender, follow-up time, and baseline BMI.  |
| 0.48   | Q2             | 1.47 (0.79-2.73) |   |
| 0.63   | Q3             | 0.83 (0.43-1.58) |   |
| 0.82   | Q4             | 1.55 (0.84-2.89) |   |
| Wang, 2007 [31]<br>Framingham Offspring Study, CRP                               |                |                  |   |
| log, 1 SD increment  | 232/1456       | 1.26 (1.05-1.51) | Age, sex, baseline systolic and diastolic blood pressure, baseline blood pressure category, baseline serum creatinine, diabetes mellitus, cigarette smoking, baseline BMI and percentage of weight change from baseline to follow-up.                             |
| Wang, 2011 [26]<br>Women's Health Initiative Observational Study, hs-CRP (white) |                |                  |   |
| 0.37 mg/L (median)   | 65/100         | 1.00             | Age, clinical center, time of enrollment, smoking, alcohol intake, physical activity, and hormone replacement therapy.  |
| 0.99   | 84/100         | 1.20 (0.74-1.93) |   |
| 2.06   | 96/100         | 1.30 (0.82-2.04) |   |
| 4.50   | 154/100        | 2.02 (1.29-3.14) |   |
| Wang, 2011 [26]<br>Women's Health Initiative Observational Study, hs-CRP (black) |                |                  |   |
| 0.48 mg/L (median)   | 82/100         | 1.00             | Age, clinical center, time of enrollment, smoking, alcohol intake, physical activity, and hormone replacement therapy.  |
| 1.37   | 76/101         | 0.94 (0.60-1.45) |   |
| 2.76   | 101/99         | 1.09 (0.69-1.72) |   |
| 7.16   | 140/100        | 1.64 (1.07-2.52) |   |
| Wang, 2011 [26]<br>Women's Health Initiative Observational Study, IL-6 (white)   |                |                  |   |
| 0.58 pg/mL (median)  | 74/100         | 1.00             |   |

# Supplementary Files

|   |         |                  |  |
|---|---------|------------------|--|
| 0.97  | 99/101  | 1.27 (0.84-1.92) | Age, clinical center, time of enrollment, smoking, alcohol intake, physical activity, and hormone replacement therapy. |
| 1.54  | 106/99  | 1.37 (0.88-2.13) |  |
| 2.78  | 118/99  | 1.64 (1.06-2.55) |  |
| Wang, 2011 [26]<br>Women's Health Initiative Observational Study, IL-6 (black)  |         |                  |  |
| 0.74 pg/mL (median)   | 73/100  | 1.00             | Age, clinical center, time of enrollment, smoking, alcohol intake, physical activity, and hormone replacement therapy. |
| 1.23  | 91/100  | 1.40 (0.89-2.19) |  |
| 1.94  | 101/100 | 1.59 (0.98-2.57) |  |
| 4.39  | 135/100 | 1.99 (1.27-3.12) |  |
| Wang, 2011 [26]<br>Women's Health Initiative Observational Study, IL-1β (white)   |         |                  |  |
| 0.13 pg/mL (median)   | 91/89   | 1.00             | Age, clinical center, time of enrollment, smoking, alcohol intake, physical activity, and hormone replacement therapy. |
| 0.20  | 84/90   | 0.93 (0.65-1.54) |  |
| 0.26  | 91/88   | 0.99 (0.58-1.68) |  |
| 0.48  | 89/88   | 1.06 (0.60-1.87) |  |
| Wang, 2011 [26]<br>Women's Health Initiative Observational Study, IL-1β (black)   |         |                  |  |
| 0.13 pg/mL (median)   | 65/90   | 1.00             | Age, clinical center, time of enrollment, smoking, alcohol intake, physical activity, and hormone replacement therapy. |
| 0.20  | 106/91  | 1.31 (0.81-2.12) |  |
| 0.28  | 98/89   | 1.42 (0.84-2.39) |  |
| 0.47  | 89/90   | 1.30 (0.73-2.33) |  |
| <b>Abbreviations:</b> BMI, body mass index; CRP, C-reactive protein; HbA1c, hemoglobin A1c; hs-CRP, high-sensitive C-reactive protein; IL-1β, interleukin-1β; IL-6, interleukin -6; IR, incidence rate; MESA, Multi-Ethnic Study of Atherosclerosis; PY, personyear; Q, quantile; SD, standard deviation. |         |                  |  |



**Online Supplementary file 6.** Funnel plot of the relative risks of 12 studies on circulating C-reactive protein and risk of developing hypertension. Begg's test  $P=0.12$ , Egger's test  $P=0.15$ . Log RR: natural logarithm of relative risk. s.e: standard error.